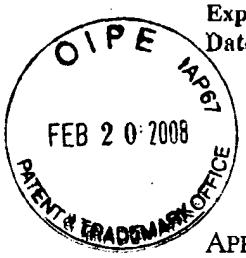
Express Mail Label No.: EV922217511US
Date of Deposit: February 20, 2008

Attorney Docket No. 34251-502 NATL




## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | | | |
|---|---|---|---|
| APPLICANTS: | Michael Philip Cohen *et al.* | | |
| SERIAL NUMBER: | 10/509,770 | EXAMINER: | Celia C. Chang |
| FILING DATE: | September 28, 2004 | ART UNIT: | 1625 |
| FOR: | Pyridinoylpiperidines as 5-$HT_{1F}$ Agonists | | |

**MAIL STOP AMENDMENT**
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

## DECLARATION OF DR. STEVEN P. SWANSON UNDER 37 C.F.R. §1.132

I, the undersigned Steven P. Swanson, hereby declare and state that:

1. I am Dr. Steven P. Swanson, Ph.D., Senior Research Advisor - Drug Disposition, Lilly Research Laboratories, a division of Eli Lilly and Company, where I have been employed for the past 19 years. My responsibilities include representing ADME functional area on cross-functional teams to provide scientific consultation and expertise, including design of plans, recommending selection of drug candidates for development, and preparation of regulatory submissions worldwide; authoring documents and presenting scientific findings to internal governance committees; contributing to the design, evaluation and interpretation of data from clinical studies, *in vitro* studies and *in vivo* animal pharmacology studies; developing, validating, implementing and/or approving appropriate analytical or enzymatic assays, methods or enhanced throughput screens used for quantification or structural identification of compounds or biomarkers, to determine pharmacokinetic or drug disposition parameters, and to determine transport or biotransformation properties, in compliance with GLP and/or OECD guidelines where required; acting as study director responsible for the design, conduct, analysis, interpretation, documentation and reporting of studies on the absorption, distribution, metabolism and excretion of compounds; and designing, interpreting and reporting

studies to evaluate the toxicokinetics of compounds in animals, in compliance with GLP and/or OECD guidelines where required. I have co-authored over 55 scientific papers in my field. See attached Curriculum Vitae

2. I am aware that the compounds as claimed in the above-identified application ("the Application") have been rejected as being obvious over the compounds in U.S. Patent No. 6,777,428 to Krushinski ("Krushinski"), taken in view of King, "Medicinal chemistry: principles and practice" p. 206-209, 1994 ("King") or published U.S. Patent Application 2006/0211734 to Blanco ("Blanco").

3. I have reviewed the available data comparing certain compounds in the Application with the comparator compounds disclosed in Krushinski. I have also reviewed the statements in the King reference and the Blanco reference.

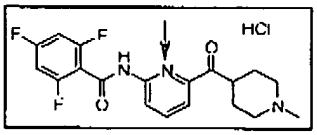
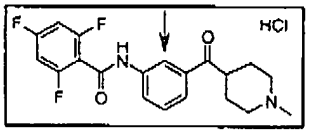
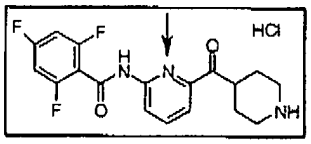
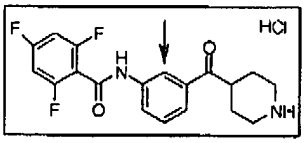
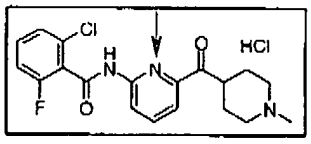
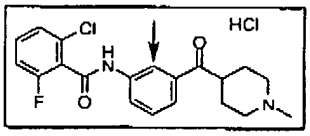
4. It is my opinion that the claimed invention is not obvious in view of Krushinski alone or in view of either the King or Blanco references, at the least because of unexpected and improved properties that have been found for the present invention.

5. The Office Action alleges that, in view of the statements in the King reference, substitution of the phenyl ring in the compounds disclosed by Krushinski with the pyridinyl ring in the compounds of the present application is obvious because pyridine and benzene are bioisosteric.

6. However, isosteric replacement is an unpredictable art and for any particular chemical modification one would expect significant differences in biological activity, which may include such properties as in vivo disposition, among others. This generally accepted principle is consistent with the actual statements made in the King reference. (See for example King, pg.209, lines 1-7.)

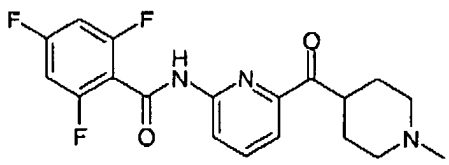
7. Research scientists at Eli Lilly and Company have conducted experiments comparing the pharmacokinetic properties of certain phenyl and pyridyl compounds, as shown in Table 1:

Table 1

| | | | | | | Liver Microsomal Extent of Metabolism | | |
|---|---|---|---|---|---|---|---|---|
| CMPD | Structure | Oral AUC in Dog 1 mg/kg dose (ng hr/ | Ratio pyridine/ phenyl AUC | Tmax (hr.) | Cmax (ng/ml) | ATSG Rat % Met | ATSG Human % Met | ATSG Category |
| A |  | 223 | 7.19 | 1 | 35.6 | 59.7 | 21.1 | Low |
| B |  | 31 | | 3 | 3.9 | 87.9 | 36 | Moderate |
| C |  | 1613 | 5.89 | 3.9 | 116 | 9 | 0 | Very low |
| D |  | 274 | | 1 | 24.2 | 40.8 | - * | - * |
| E |  | 117 | 1.60 | 2 | 15.7 | 86.5 | 15.8 | Low |
| F |  | 73 | | 1.5 | 8.33 | 94.9 | 31.4 | Moderate |
| | Dog exposure N=2 | | | | Liver microsomal data; N=1; * No value due to interference in assay | | | |

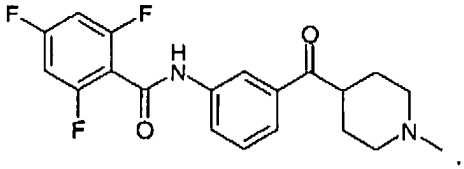
8. Research scientists at Eli Lilly and Company have conducted experiments comparing the pharmacokinetic properties of certain compounds claimed in the Application (Compound **A**)

**A**



with the properties of the Krushinski compound cited by the Examiner (Compound **B**)

**B**



9. For 5-$HT_{1F}$ agonists which are candidates for treating and/or preventing migraine, rapid oral exposure of pharmacologically active amounts of compound is an important criterion.

10. The oral exposures for the compounds **A** and **B** (HCl salts) were compared using a standard dog study, and were found to be dramatically and unexpectedly different.

11. For Compound A, the oral exposure in dogs as measured by the area under the curve (AUC) was 223 ng·hr/ml. By contrast, the oral exposure for the Krushinski Compound, B, gave an AUC of only 31 ng·hr/ml.

12. Likewise, the peak plasma concentrations ($C_{max}$) were dramatically different with Compound **A** having a $C_{max}$ of 35.6 ng/ml and the Krushinski Compound **B** having a $C_{max}$ of only 3.9 ng/ml .

13. In addition, the in vitro metabolisms of Compounds **A** and **B** were examined in human liver microsomes as a surrogate for clearance in humans. Compound **A** demonstrated reduced metabolism compared to the Krushinski Compound **B**.

14. Similar comparisons of Compound **C** (essentially as in example 8 or 17) vs. Compound **D** (within the scope of Krushinski) and Compound **E** (essentially as in example 4) vs. Compound **F** (within the scope of Krushinski) show similarly superior results for the compounds of the present invention over the Krushinski reference. (See Table 1.)

15. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that willful false statements may jeopardize the validity of this application and any patent issuing therefrom.

Dr. Steven P. Swanson

Signed this 20 day of Feb, 2008